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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,418	10/07/2003	H. Michael Shepard	NB 2008.01 (060925-0801)	7416

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EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,418	SHEPARD ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/29/2005 (amdt)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-61,63,64,68-70,73-75,78-80 and 83-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-61,63,64,68-70,73-75,78-80 and 83-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **65-67, 71-72, 77 and 81-82** have been cancelled, claims **53, 55-56, 63, 73-75, 78-80, 83-84 and 86** have been amended, the disclosure has been amended to correct imaging and substantive errors, and no new claims have been added as per the amendment filed November 29 2005. One Information Disclosure Statement (IDS) filed November 29 2005 has been received with all cited references. The two additional references not cited on the PTO-1449 but provided, are noted and made of record on the attached PTO-892.

Claims **53-61, 63-64, 68-70, 73-75, 78-80 and 83-93** remain in the case. Examiner notes that the list of claims remaining under examination differs from the instant list found in applicant's response at page 18 (claims **78-80** not listed by applicant).

In re applicant's response to the request for an explanation concerning the extensive listing of references the vast majority of which were not directly relevant to patentability of the instant claims, examiner notes applicant's explanation. Examiner also notes that the most recent submission is, with the exception of two references which mention the "NB1011" compound, are also not closely related to the instant claimed subject matter. Examiner respectfully requests limitation of submissions to references disclosing subject matter directly relevant to issues of patentability only.

The disclosure is objected to because of the following informalities:

At page 41, at line 29, the term "uricil" (both occurrences) is a misspelling of -- uracil --.

At page 55, line 26, the term idodide" is a misspelling of -- iodide.

At page 56 at lines 3 and 4, the term "N-methoxy-L-alanine" implies that the alanine derived compound being used in the subsequent synthesis include the functional group " -NH-OCH_3," when in fact only the methyl ester of alanine is listed as a reactant and there is no subsequent chemical step wherein the "OCH_3" group could have been added. See also page 56 at line 21 and page 57, line 14 wherein the identical error has been repeated.

Appropriate correction is required.

Applicant's arguments with respect to the disclosure have been considered but are deemed to be moot in view of the new grounds of objection.

Claims **53, 55, 56 and 63** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments with respect to claims **53, 55, 56 and 63** have been considered but are deemed to be moot in view of the new grounds of rejection.

In claims **53, 55, 56 and 63** the term "and optionally bound to the 3'-carbon of the sugar through its carboxy group" is new matter because said term has not been found to occur anywhere within the specification. In addition there is no showing of the isolation or characterization of any compounds of including the described structural feature identifiable by examiner within the listings of specific embodiments.

Applicant's arguments with respect to claims **53, 55, 56 and 63** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **53-61, 63-64, 68-70, 73-75, 78-80 and 83-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed enabling exemplifications.

The instant claims are directed to all "N-amino acid" substituted nucleoside phosphoramidates when the instant disclosure only discloses how to incorporate a single amino acid (alanine) as a substituent in the claimed phosphoramidate. Examiner assumes said claimed compounds and methods are outside the scope of the disclosure until amendments or explanations clarify the matter sufficiently to the contrary. The suggested listing should be added by amendment to the disclosure and will not be rejected as new matter so long as clear evidence is submitted establishing that the molecular structure of each "NB" compound not previously identified in the disclosure was known to applicant prior to the earliest filing date.

Claims **63-64, 68-70, 74, 78-80 and 83-93** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims extends to compounds the synthesis of which has not been defined in a manner permitting one of ordinary skill to know the identity of the compounds which have shown activity in the treatment of neoplastic disease conditions. In addition, claim **63** identifies compounds the synthesis and biological testing of which has not been disclosed, including
i) wherein "R^1 includes as a terminal substituent CN,"
ii) wherein "R^7 is a ... a phosphoramidite group" wherein the amino acid substituent is other than N-alaninyl or a carboxylate ester thereof,
iii) "wherein the compound may be in any enantiomeric, diastereoisomeric or stereoisomeric form, including ... L-form, α-anomeric form." Only D-forms are disclosed as having been synthesized and as having the desired medicinal activity, and
iv) because there is no showing of either how to make or use the compounds defined by claims **83 and 84**.
In addition, applicant has not supplied any data to support the extension of treatments to include "liver cancer."

B. The nature of the invention is directed to 5-substituted-2'-deoxyuridines and analogues thereof as defined by claim **63**, pharmaceutical compositions thereof, a method of testing for relative antineoplastic activity, and method of treating several different neoplastic disease conditions.

C. The state of the prior art is well established by the extensive lists of prior art patents and other references disclosed by the patents issued to Shepard and Shepard et al. listed on the instant PTO-892.

D. The level of one or ordinary skill is high because the practice of the invention requires knowledge of both the organic synthesis of nucleoside analogues and the medical knowledge

and training required to properly administer and monitor antineoplastic agents to a host in need thereof.

E. The level of predictability in the art is limited because the number of compounds actually synthesized and/or tested, and the specific disease conditions tested, is very small when compared with the number of compounds included within the scope of the instant claims. In view of the lack complete test data, it is also unclear that the substitution of "Cl," "I" or particularly the pseudohalogen "CN" for "Br" as an X-substituent will produce equivalent biological testing results. Similarly, most of the variations provided for by the alternatives within the definitions of variables R^6 and R^7 have neither been synthesized nor tested for biological activity. And, only three neoplastic cell types have been shown to be effectively inhibited. For this reason examiner concludes that the asserted and claimed extrapolation to the effective treatment of all "pathological" cell types which overexpress thymidylate synthase is not sufficiently predictable and therefore not adequately enabled.

F. The amount of direction provided by the inventor is difficult to determine because of incomplete synthetic information and incomplete identifying information concerning the identity of compounds tested for biological activity at pages 68-69. Applicant has not provided enabling support for the synthesis of "any enantiomeric, diastereomeric or stereoisomeric form," and in particular has not shown how to make the L-forms and the α-anomers of any of the claimed compounds, or shown that the asserted and claimed pharmaceutical activity or testing for said activity of claims **59-61 and 87-93** extends to all possible enantiomers and diastereomers and other than ß-D-isomers of some of the compounds defined by claim **63**.

G. The existence of working examples is difficult to determine because of incomplete identifying information concerning either the synthesis of many of the compounds claimed or the identity of compounds tested for biological activity at pages 68-69.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in light of the very limited amount of biological test results and synthetic instructions provided for the compounds defined by claim **63**. In particular, the instant method of treatment claims are only enabled for the treatment of one variety of breast cancer, one variety of colon carcinoma, and one fibrosarcoma (HT 1080; organ apparently not specified in the disclosure) according to the table at page 70. There are

no enabling examples for the claimed method of testing. Therefore, examiner concludes that the amount of experimentation required to practice all aspects of the instant claimed invention is undue in view of the lack of anything but prospective disclosure.

Applicant's arguments with respect to claims **63-64, 68-70, 74, 78-80 and 83-93** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **53-56, 63 and 78** is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **53, 55, 56 and 63** the term "substituted phenoxy" renders the noted claims incomplete because said term fails to be defined further by definitions of what phenoxy "substituents" may be optionally present.

In claim **54** the term "comprised of" renders the noted claim incompletely defined because the noted term implies the presence of additional undefined compounds which are also being claimed. Said term also renders the instant claim lacking in proper antecedent basis because the parent claim **53** has a narrow scope and claim **54** includes subject matter not defined by the parent claim, a view confirmed by the term "halogenated" when only -- bromo -- is found in claim **53**. And lastly, in view of the wavy bonds to the terminal H and Br substituents of the diene side chain in the structure at line 2, the instant claim, if read narrowly, fails to further limit the subject matter of the parent claim and is therefore improperly dependent.

Claim **58** should be re-written as follows:
-- A pharmaceutical composition comprising a compound of any one of claims **53 to 56** and a pharmaceutically acceptable carrier. --
because otherwise the noted claim is improperly dependent from the parent claim which claim by definition possesses a broader scope of coverage. Alternatively the noted claim is indefinite because the claimed subject matter is defined simultaneously by terms having two different scopes; i.e. "composition" is more expansive in scope than "pharmaceutical composition."

In claim **78** the dependence is improper because a compound claim is confusing when it depend from either a compound claim (**63**) or a composition claim (**57**)as presently drafted.

The instant claim should also begin with the term -- The -- when dependent from another compound claim. Examiner suggests amendment of the preamble to read -- The compounds as defined in claims **57 and 63**, ... --.

Applicant's arguments with respect to claim **53-56, 58, 63 and 78** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **88, 89 and 90** are objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims to place the claims in proper dependent form.

Examiner suggests that the "method" claims noted should properly depend from "method" claim **87**, not "pharmaceutical composition" claim **86**.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **63-64, 73-75, 78-80, 85-86 and 91** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***1-10*** of U.S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical,

they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed November 29, 2005 have been fully considered but they are not deemed to be persuasive.

Applicant has deferred responding to the instant grounds of rejection pending a finding of allowable subject matter.

Claims **53-61, 68-70, 83-84, 87-90 and 92-93** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. §112.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published

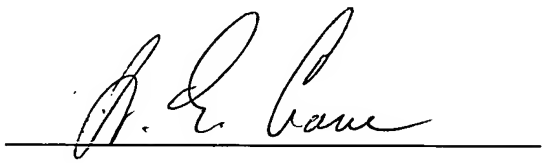
in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX directly to Examiner's computer is 571-273-0651. Telephone number for filing documents officially with the USPTO is **703-873-9306**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
01/12/2006



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